

International Breast Cancer Foundation
Background Report

Breast Cancer:

Seeking Answers to a Worldwide Problem

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Why is progress in preventing and curing breast cancer so slow? A discourse addressing this question and proposing some directions for efforts to speed up progress must start by acknowledging that its premise is true: progress is indeed slow. At an individual level, I see it in my clinical work with women concerned about their risks for developing breast cancer and with women who suffer from this disease. Over the last 20 years, what I can suggest that women do for themselves and what I may recommend as interventions have remained basically unchanged and are likely to have only limited impact. There are many letters and telephone calls from former patients, combined with information about patients' outcomes gathered in my research, which prevent me from having any illusions about the extent of significant progress. The complicated statistics of cancer, when the selected, politically motivated data are put in context, confirm the conclusion. But I enter those encounters with patients and activities concerned with new research proposals with optimism because I believe that in many respects we know more than we have successfully communicated to the public and more than we have applied to women's well being. Further, I believe that a thoughtful look at breast cancer as a global problem offers explanations and directions which are hopeful. Accepting the truth -- our lack of progress -- can help us do what Michael Sporn has challenged us to do: "develop new approaches to control this plague of deaths . . . based on a more sophisticated understanding of the process of carcinogenesis and the potential to prevent disease before it becomes invasive and metastatic." [see Sporn MB. *The Lancet* 347:377-381, 1996]

Numbers worldwide and American

While we are assaulted with numbers, it often seems difficult to get answers to basic questions about breast cancer. On a global stage some dimensions are these: 1 million new cases each year; a woman dies of breast cancer every two minutes somewhere on the planet; the majority of newly diagnosed women are premenopausal. This last fact often comes as a surprise because in the United States about two-thirds of new diagnoses are in postmenopausal women. The brief explanation is that, while the frequencies of breast cancer (the incidences) in Western countries are higher (in younger women and very much in older women), the huge young population of Asia -- China, Indonesia and India -- develops more cases.

The most basic measure about breast cancer is its frequency. The key number is the incidence: the number of newly diagnosed cases per 100,000 (usually) per year. It seems to be a deceptively easy number to develop. While ascertainment of all breast cancer cases in a population presents some challenges, the more difficult issue here is getting an accurate estimate of the population -- the 100,000s in which these cases occur. The debates about the accuracy of the census data in the United States reflect such difficulty. Since breast cancer increases in frequency -- incidence -- with increasing age (see Figure 1, curve A for Caucasian women in the United States), the age make-up of the "population" used to estimate an overall, so called age-adjusted, breast cancer incidence figure is important. Figure 2 shows incidence data over 20 years from a United States registry program which covers about 10% of the population, using as a descriptor of the population 1970 United States data. For many reasons, this figure probably gives us an accurate answer to the usual basic question about recent trends in frequency in the United States, but note that the data presented are for Caucasian women, for invasive cancers only (while the frequency of non-invasive cancers -- often but not always the precursors of these -- has been increasing rapidly recently), and are believed for the most recent times (and probably

also for earlier years also, but perhaps not to the same extent) to underestimate the actual incidence numbers by 3%. Additionally, and not shown by this figure, most of the recent increase in incidence is due to increased incidence in women over age 50. If we accept this trend figure as "truth," what does it tell us? It appears that in the 1980s there was a rapid major increase in breast cancer incidence, with a readjustment of the rate at a significantly higher level through 1993. So, yes, breast cancer has been increasing in incidence in the United States, and the rate now seems significantly higher than it was 20 years ago.

The next question, of course, is What might explain this pattern? Here we get into even trickier territory. Two circumstances appear to have contributed to the 1980s increase. First, overall, more women were either not having children at all or having them at older ages. These women are at greater risk for breast cancer as will be discussed further below. Second, greater and greater fractions of women in the 1980s were undergoing mammography with nearly detection of small breast cancers sooner than might usually occur. More refined questions follow logically from these ideas: in particular, if these are true explanations for the increase in incidence, what do these circumstances forecast for future trends in incidence? Let me stop this exploration of incidence trends here, however, because these explanations are at best probably only partial, and the general picture provided by incidence data can only take us this far: overall breast cancer incidence continues to be high and some priority should be placed on achieving a comprehensive understanding of why.

While incidence is a basic measure of breast cancer frequency, it describes only part of the story. A second bottom line measure is needed: mortality. Here there is good and bad news. Overall, very recently in the United States, mortality from breast cancer has been declining. Some details are more illuminatory than an overall age-adjusted figure (like the one for incidence). As the 3 figures (Figure 3 A, B, C) show, recent decreases are seen in three middle-

age decade groups. Note that the 1993 rate is the same as that in 1975 for women 60-69 at death, while decreases of 18% have occurred in the mortality rates for women 50-59 and 40-49. The decrease in an overall mortality figure (not shown) is much more modest because older women have not had decreased rates at all. An overall figure describing the mortality trends in England and Wales shows a recent decrease also (Figure 4). This recent pattern of decreasing mortality is, however, not seen in most of 20 countries in Europe, North America, Australia and New Zealand, where in half an increase and in half no change in mortality is seen over the last 40 years [see Hermon C and Beral V, British Journal of Cancer 73:955-960, 1996]. While credible data are sparse, I suspect that in most other countries of the world, mortality from breast cancer is increasing. In sum, there are some improvements in very recent mortality figures in the U.S. and England, but the mortality rate remains high, and in most of the world it is actually increasing. Additionally, of some interest and unexplained is the discrepancy between trends in incidence and mortality in the United States [Figures 2 and 3], with incidence increasing while only very recently mortality is decreasing. A favorable interpretation of this discrepancy is that we are doing much better in treating a more frequent disease. Other data indicate that mortality from breast cancer in women 55 and over gradually and significantly increased in the 15-20 year period prior to 1990 despite more early detection by mammography and better treatment. Additionally, there was a major decrease in mortality from breast cancer in women 54 and under between 1970 and the early 1980s [see Bailar, J New England Journal of Medicine 336:1569-1574, 1997]. There are no clear explanations for these trends. Many other factors may be contributing to this mortality picture, however, as considering what we know about causes, early detection, and first treatments makes clear.

An overview of current knowledge about causes, prevention, early detection, and treatment

CAUSES

Much current writing about the causes of breast cancer concerns the discovery of genes with specific mutations whose presence confer markedly increased risk for this disease. At present, how these changes operate to cause breast cancer is unknown, and the future impact of this discovery on occurrence or management of breast cancer is clouded. It is likely that the impact of these discoveries will be spun out over many years, if not decades. A more long-standing theme in discussing the causes of breast cancer has been that we have no ideas. In great part this appears to be because there have not been single, well-supported, manipulable "causative" factors identified which are important in large numbers or even fractions of cases. In sum, because there appears to be little to do, there is thought to be little known. Considerable biological and epidemiologic data and a global perspective suggest that, in fact, the opposite is true and that these data should provide significant direction to our research.

That breast cancer, from the time of its inception, develops over many (perhaps 10-20 or more) years has been suspected for a long time, and that its developmental biology is complex has also been obvious. Statisticians have interpreted the rapid and marked linear increase in the age incidence Figure (1) (first part of curve A) as suggesting that 4-6 successive genetic changes are necessary to produce a clinically evident cancer, with the later-acquired changes likely the ones which confer the ability to invade and spread. Some epidemiologists interpret the early-in-life linearity in this curve to suggest that breast cellular changes must occur in those early years which have a profound impact on later occurrence of breast cancer. In sum, based on many data, development of breast cancer in multiple steps over many years is clearly likely.

The breast cancer age-incidence curve (for Caucasian American women shown in Figure 1A) is profoundly different in different groups of women (see curves B and C), and these observations are key to concluding that we do understand a great deal about why this disease

develops with much greater frequency in some women. Breast cancer is a hormonal -- estrogen-produced -- disease. Based on well-accepted epidemiologic data, Pike and colleagues have estimated that women undergoing removal of both ovaries at age 35, with marked lowering of tissue estrogen levels, have a markedly lower incidence of breast cancer [curve B, Figure 1] [see Pike MC. British Journal of Cancer 60:142-148, 1989], and consistent with this observation it is known that for many, particularly Asian, populations with known lower estrogen levels, the age-specific incidence curve is like that shown in curve C [Figure 1]. The fact that the curve (A) changes slope around the time of menopause, a time of profound hormonal change also, provides indisputable proof of the adverse role of hormones. Note that each of the axes in this figure is logarithmic so that the numerical differences implied in these three curves are huge: an average Asian woman at age 40 has a risk of breast cancer of 25/100,000 each year while an American woman's risk is 4 (or more) times greater at 100/100,000; at age 60 an Asian woman's risk is but one-sixth of that of American women. Between other specific groups of women (not illustrated by these figures), the magnitudes of differences in incidence are even greater -- 8- to 10-fold. These great differences in frequency of breast cancer are generally agreed to be a consequence of major hormonal and not genetic, i.e., hereditary, differences in these populations.

Identifying the initial factors which damage duct cells has been a major focus of breast cancer epidemiologic studies (Box I, Table 1). For some time, as a result of follow-up studies of young women exposed to radiation who survived the atomic blasts at the end of World War II or women who had repeated X-ray evaluations for tuberculosis, and more recently as a result of follow-up studies of young women treated with radiation therapy for Wilm's Tumor (of the kidney), Hodgkin's Disease and other benign conditions (acne or asthma, for example), it has been clear that radiation to prepubertal and adolescent breast tissue is an important cause of cancer. Some data suggest that cigarette smoking (active or passive), particularly in adolescence (in which group of women this habit is unfortunately increasing), is also a risk factor. Other new

data suggest that hormonal conditions around childbirth are important in determining risk for breast cancer many years -- indeed decades, later. Beyond these three (and possibly inherited genetic mutations), initial breast cancer causes are not identified. Some epidemiologists maintain that explaining the age-incidence curve does not require any other initial causes, while many seem unconvinced that all significant initial causes have been identified.

Of major interest is how many "risk factors," conditions, or hormonal changes associated with breast cancer explain its development. The long development period and the multiplicity of necessary changes have obscured the emerging broad picture of the two proximal or direct "causative" circumstances for this malignancy. There are essentially two: 1) (increased) cumulative exposure of breast ductal cells to growth-stimulating hormones, particularly estrogens; and 2) (longer) duration of time when undivided and sensitive breast cells are present to be injured or to accrue one or more genetic changes. The sequence of factors, and changes leading to these two important causes are highlighted in Table 1, Boxes II and III. Caloric intake (and possibly the sources for calories) and level of physical activity during the prepubertal years influence the age at which adolescent girls begin menstrual cycles. In general, an excess of calories over expenditure and low levels of exercise are believed to be the habits with this consequence. Early age at first menses is associated (progressively more for each earlier year) with critical long-standing changes in menstrual and hormonal fluctuations: shorter duration of menstrual cycles and more cycles per year. Vigorous exercise arrests menstrual cycling once begun also. These changes thus affect the frequency with which sensitive breast ductal tissues are exposed to the major fluctuations in estrogenic hormones which are part of normal menstrual cyclicity. Many other identified or suggested (indicated by ? marks in the table) risk factors also likely operate through mechanisms which similarly affect the cumulative exposure of breast tissue to estrogen. The impact of early age at oophorectomy shown in Figure 1B and, generally, geographic differences in breast cancer risk-factor frequencies are very consistent with this

interpretation.

The second sequence of events critical in the development of this disease is somewhat less complex [see highlighted Box, III, Table 1]. Age at first full-term pregnancy is directly and strongly related to breast cancer risk [Figure 5]. In a series of elegant studies, Jose and Irma Russo have provided the physiologic explanation: a full-term pregnancy causes breast duct cells with the potential for division to acquire permanent non-dividing status [see Russo J, Russo IH. Cancer Epidemiology Biomarkers and Prevention 3:353-364, 1994]. Before a pregnancy these cells appear more sensitive to damage, beside being capable of propagating a series of damaged cells. Thus, if the length of time between first menstrual period and first full-term pregnancy is many years, say 20, this creates a greater opportunity for breast cells to be damaged. All hormonal risk factors act on the pool of ductal cells [Table 1].

I believe there are two clear messages about causation of this disease: First, the big (immediate physiologic) causes of breast cancer are known, and second, international differences in risk factors and occurrence of disease have been critical in elucidating the broad developmental picture.

PREVENTION

Prevention of breast cancer might most logically follow from knowledge of causes and risk factors. The complex biology and chains of causal events reviewed above identifies only a few (easily) manipulable risk factors, and this has encouraged the search for other specific active interventions. Clearly, proscription of excess calories, alcohol, and tobacco and adoption of a moderately vigorous exercise program/lifestyle seem appropriate and likely beneficial.

Like the media attention given to genetic mutations as an important cause of breast cancer, attention to the investigation and use of tamoxifen, an oral antiestrogen hormone, in the prevention of breast cancer seems disproportionate to its likely usefulness. I have argued in

another communication that the large American study of tamoxifen in healthy women at risk for breast cancer is premature, ill-conceived and unlikely to provide the kinds of answers about this hormone truly useful to women [see Love RR. Cancer Epidemiology Biomarkers and Prevention 2:403-407, 1993]. A key issue here is what the other adverse consequences or costs of this treatment are. It's the downsides of this treatment which are critical.

EARLY DETECTION

The earlier comments about the multi-year natural history of breast cancer place in context a discussion of early detection of this disease, that is detection before the disease produces signs or symptoms of a breast problem which cause a woman to seek medical attention resulting in a diagnosis. Clearly, if breast cancer develops over 10-20 years, any detection clinically is "late." What is relevant and somewhat startling is that, in fact, with mammography - X-ray imaging of breast tissues -- preclinical breast cancer can often be identified, and that on balance in women older than about age 50, such early detection-"screening" tests are associated with decreased risk of dying of breast cancer.

The particular challenges of early detection with mammography are in younger -- premenopausal women -- where, I would suggest, in some senses mammography works too well. The problem is the following, most dramatically illustrated by Virginia Ernster and her colleagues [see Ernster VL. Journal of the American Medical Association 275:913-918, 1996]. The markedly increased use of mammography during the 1980s in the U.S. in younger women has led to a large increase in diagnosis of breast abnormalities called ductal carcinoma-in-situ (cancer in place) (DCIS) (non-invasive breast cancer), heretofore believed to be inevitable precursors of invasive breast cancers. Women with this diagnosis are usually treated with breast removal -- mastectomy -- which is almost always curative. The problem is that the numbers of DCIS cases being diagnosed appear far in excess of the numbers of invasive cancers to be

expected without mammography, and thus "most of the DCIS cases being diagnosed today might never have surfaced (i.e., developed to being invasive breast cancers and diagnosed) in the absence of mammography" [Ernst VL, et al. JAMA 275:918, 1996]. In sum, screening mammography in premenopausal women appears to often diagnose DCIS (-like) abnormalities which might never progress to be problems but which are being treated aggressively with mastectomy. On balance, it remains unclear for large groups of women, whether this early detection effort benefits more women than it harms. Again, as for tamoxifen, the issue is the costs -- the downsides for the women who get over-treated with unnecessary mastectomies (and not financial "costs" of screening tests which some proponents of screening have maintained). For the present, we have no good way of distinguishing the "good" ductal carcinomas in situ (DCIS) which will never progress, from the "bad" DCIS cancers which need treatment, so we treat them all the same.

TREATMENT

From a patient's perspective, the treatment of invasive (i.e., serious) breast cancer over the last 25 years is also a good/bad news story. The proven equality of benefit from lesser surgical procedures, which preserve most of the breast tissue and major chest muscles, has made the usual primary treatment [now "lumpectomy"] less disfiguring for many women. Additionally, for those taking chemotherapy, the development and use of remarkably effective anti-nausea and anti-vomiting medicines has lessened the immediate toxicities from this type of therapy. The sum of the bad news was essentially reviewed earlier in noting the limited and very recent improvements in mortality, despite major, widespread, aggressive use of several systemic therapies. Key aspects of the development, nature and impact of systemic therapies deserve some thoughtful review. The history of the last quarter century of systemic (i.e., whole body) treatments for breast cancer follows most from experience with human leukemias -- blood cell cancers. In the late 1960s and early 1970s, two schools of thought came together. The first was that despite clinical absence of evidence of spread of breast cancer to distant organs and tissues at the time of diagnosis, many women have such "micrometastases" which eventually grow and can kill them. Thus, for many women breast cancer is already a systemic disease at diagnosis; that is, it has already often spread beyond the breast when it is first diagnosed. Second, in animals it became clear that to achieve cure required killing the last cancer cell, and cytotoxic-chemotherapy drugs, particularly when used in combination, were successful in achieving this goal. Successful experience with human leukemia suggested that the same results could be obtained in other human cancers.

Studies of adjuvant chemotherapy (additional treatment at the time of breast cancer diagnosis) were launched based on these ideas, and these treatments have shown some benefits. As these benefits have been only modest, however, extensions of the leukemic laboratory observations have led in recent years to more intense chemotherapy treatment programs, and herein lie some important observations. Table 2 outlines a current national adjuvant

chemotherapy study. To even the nonexpert observer, it is obvious that this study is addressing a large number of questions (and some elements have been left out here). A treatment here can involve different doses and schedules of 3 different chemotherapy drugs (all given intravenously), one or more anti-nausea drugs, a growth factor protein to stimulate white blood cell numbers, an antibiotic, and blood transfusions. I believe that the technical complexity, toxicities, and financial costs of such treatment programs compromise significantly their efficacy, acceptance, and usefulness for most women with breast cancer. This statement bears some amplification. The graphic results from a standard adjuvant chemotherapy treatment program for breast cancer are shown in Figure 6. Treatment was given with three drugs, CMF -- cyclophosphamide, methotrexate, and 5-fluorouracil -- for six or twelve months in the immediate period after diagnosis and mastectomy. The vertical axis notes the likelihood that different groups would be alive; for example, 0.5 means that one half of all people in that group were alive at the time point indicated on the horizontal years axis. The planned doses of the three chemotherapy drugs given were calculated using a schedule by which doses are individualized according to body surface area. The "control" group is of women who received no chemotherapy initially. The survival experience of this untreated group says that after 5 years 70%, at 10 years about 47% and at 20 years about 25% were still alive. In contrast for patients in the CMF-treated group who received greater than 85% of planned doses, the survival experience is remarkably better: 80% at 5 years, 67% at 10 years and 50% at 20 years. The survival experiences of two groups of CMF-treated women receiving less than 85% of planned doses are however not meaningfully (that is not statistically) different from that of untreated women. Finally, and most critically, only 20% of women selected to receive CMF actually were able to receive more than 85% of planned doses. This small percentage developed primarily because of bone marrow-blood cell and gastrointestinal effects of the drugs severe enough to strongly justify dose reductions. These results have major implications for widespread use of this and similar

treatment programs and suggest why their efficacy may be limited for large numbers of women. This brings us back to current national studies, many of which look like that shown in Table 2. Current studies are addressing interesting biological questions, but I am unconvinced that they have the potential to define new therapies likely to be effective for most women, both in this country and in the world, needing treatment. It is worth noting that contrary to common perceptions, the cancer recurrence experiences of pre- and postmenopausal women with breast cancer are equivalently bad; cancer is not more indolent in older women. For a variety of reasons, the dominance of the leukemia model in new treatment programs may be waning. Long-term favorable experience with hormonal treatments in breast cancer and laboratory studies about factors important in growth of disseminated cancers are fostering a new model in which "control," and cancer cell "dormancy" are the watch words. But let me return to this shortly.

The discussion so far has focussed on adjuvant treatment -- presumptive treatment. Many women, however, face circumstances where clinical evidence of cancer spread is present and here the disease is clearly not curable using any current methods. It is important to consider that these circumstances, where tumor-metastases are present, represent the culmination of cancer development. The cells in these metastatic satellite tumors are hardy survivors with multiple genetic changes facilitating their survival against the host and any therapies. Treatment in these circumstances is significantly challenging. Nevertheless, control of such tumors is sometimes possible. Disease stability or long-term remissions are seen in many cases, whether because of the inherent characteristics of the specific tumors a patient has, or sensitivity to the particular interventions a patient receives. It is possible that "tailored" treatment approaches can often achieve very meaningful results for patients with such metastatic breast cancers, when particular characteristics of the individual tumor are targeted.

Priorities for progress

The foregoing discussion has suggested that any advances in control of breast cancer have had only a recent and modest impact on mortality from this disease in a few Western countries, that causes are better understood than is often stated but that preventive strategies are currently limited in number and fractions of women to whom any apply, that early detection with mammography in premenopausal women is more problematic than is commonly discussed, and that initial systemic (adjuvant therapies) are significantly complex, toxic, and expensive, while providing major benefits to only a minority of treated women. These conclusions and global and public health perspectives suggest what priorities should logically follow from these realities.

Historically, understanding disease causes and development in detail has been the key to significant advances in control, and so it probably will be for breast cancer. Thus the major priority should be in this area, and special populations around the world are likely to be the most

useful in getting answers faster here.

A second key broad priority is that in treatment, public health perspectives are likely to be critical to achieving gains in population measures of progress -- in decreasing mortality.

The current individual disease-based approach which dominates efforts in the United States has led to technically complex, extremely toxic (and unacceptable), and high cost interventions. The push for complex therapies to combat this often lethal disease has somehow kept us from broad perspective on what is really likely to help larger numbers of women. I would argue that a large fraction of clinical treatment studies at present is unlikely to provide useful results for many women. In treatment our greatest efforts should be with treatments at the time of diagnosis. The progressive changes in breast cancer cells, as the process in an individual patient develops over time, lead to tumors which have significant growth advantages. Thus in a patient with many such tumors in different parts of her body (that is, a woman with metastatic cancer), the therapeutic challenges are daunting, and the long-term impact of any therapies is likely to be low. In contrast, the biological circumstances at the time of initial diagnosis present considerably more opportunities and a greater likelihood for achieving a significant impact, and developing new approaches to treatment at this time should be a major focus.

A third priority that follows our generally unsatisfying state of breast cancer control is research, and particularly clinical research. In business it is well recognized that "R & D" -- research and development -- are absolutely key to success. It is hard to estimate precisely, but perhaps 5% of the total dollars spent on breast cancer in the United States annually, goes to research. This low percentage to R & D in a business would be read a formula for failure. There has been a major increase in U.S. breast cancer research funding over the last 4-5 years, perhaps a 5-fold increase; however, this increase has been almost exclusively in laboratory-based projects. A review I made of current government and other large state and foundation funding

projects in breast cancer suggests that perhaps 80% are laboratory based. In the long-term, clearly basic science-laboratory discoveries and progress will be key to the development of better clinical interventions, but I would argue that the current balance of laboratory and clinical research is significantly wrong. Clinical studies give new ideas for laboratory ones and all too frequently indicate how irrelevant laboratory results are for patients.

In the endeavor to increase clinical research, we must somehow address the bureaucratic, economic and organizational barriers which are paralyzing the process in the U.S. Too often business considerations influence the types of studies being done. Partnerships with colleagues in other countries offer one approach, but here in the U.S. there is a desperate need to make clinical research an integral part of clinical care. Cost-control efforts by health insurers and in managed care plans often prevent participation in clinical research. And finally with respect to this research priority, we need to be more interested in the potential overall usefulness from our tested interventions. At present many clinical studies in breast cancer appear likely to show some benefit and to provide some useful information (the complex study described in Table 2, for example), but the application of these results to large numbers of women is questionable. Our studies are often "me toos" when what is needed are "breakthroughs."

This discussion of priorities may be easier to accept in the abstract; let me move to making specific observations and suggestions for new directions in breast cancer built on these priorities, which I believe make sense and offer grounds for optimism.

New directions

We need a new agenda to combat the slow progress against breast cancer. The problem is global, and so also should the solution be. The challenges to finding successful interventions are great; our efforts should be bold, and grounded in our best biological science whenever possible. Our major efforts should be in understanding causes; developing first treatment approaches which are simple, nontoxic and inexpensive; and clinical research. First, we should launch major research studies of the determinants of hormonal changes, particularly menarche in adolescent girls, and of the impact of changes in the identified factors. As suggested earlier, the balance of caloric intake and exercise seem important; longitudinal studies of homogenous populations in different countries -- in Asia, in Latin America, and in the new independent Baltic states, for example -- are likely to be significantly enlightening. Studies of other modulators of hormone levels and action, of more "ideally" constituted oral contraceptives, as are being currently done by Malcom Pike and colleagues, should also be increased, as should investigations of ways of "tricking" undifferentiated breast ductal cells to differentiate as they do with a full-term pregnancy, to decrease further sensitivity to carcinogens. The roles of other exposures, pesticides, fertilizers, in utero hormonal exposures, and tobacco should be investigated for large well defined exposed groups; again, often such populations will be in other countries. In short, as a first priority, global epidemiologic research in breast cancer should be significantly increased.

Next, the emerging biologic data point to a new framework and ways to control breast cancer, particularly when tumors are small, at the time of diagnosis (see Schipper, Turley and

Baum. The Lancet 348:1149-51, 1996). We need to increase our numbers and types of first-treatment breast cancer research studies. For the last 20 years, for example, there has accumulated an increasing body of data about the favorable and permanent impact of limited term tamoxifen -- the antiestrogen hormone -- treatment on breast cancer growth. This experience and data emphasize that in fact growth control can result in long-term disease control. During this same period in the laboratories of Isaiah Fidler and Judah Folkman, studies have suggested the critical steps in cancer metastasis -- cell dissemination, implantation and angiogenesis (growth of nourishing blood vessels into a newly growing tumor). It is cancer spread -- metastasis -- which kills women with breast cancer, but the process is remarkably inefficient. These observations have provided some biologic underpinnings for attempts to minimize these dissemination, implantation and angiogenesis stages. It is now reasonable to propose and carry out clinical research studies to test some intervention ideas. Given the various barriers in the U.S., in some cases such clinical research studies may be more rapidly accomplished in other countries where less confounding from other treatments and lower costs prevail. Specifically for example, protease inhibitors given at the opportune time may interfere with tumor dissemination, while anticoagulants and other anti-angiogenic agents may prevent early growth of micro tumors. In particular, such new interventions should meet our public health tests of technical simplicity, low toxicity, and potential for low costs.

Yes, other new directions -- in genetics, in early detection, in exploiting pharmacology to increase the therapeutic indices of currently available therapies -- should be pursued, but I would argue that, if in our generation we are to really challenge this deadly disease and change the numbers, the emphases indicated are more likely to be productive courses. And along the way we need to use opportunities worldwide to get answers for us all: a rising tide lifts all boats.

Further reading

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Table 1

Associations ("Risk Factors") for breast cancer and how they work as "causes"

	Association or "risk" factor	Mechanism for affecting <u>likelihood of breast cancer</u>	Cause
I	Family history of breast or other cancer in close relatives	Change(s) in gene(s) important in breast cell growth (and repair of damage to genes?)	?
	Cigarette smoking		Direct damaging effect on DNA in genes of breast cells
	Radiation treatment		
II	Balance of dietary calories	Age at first menstrual period	
		Younger age at menarche more and shorter menstrual cycles	
		[Intense exercise missed menstrual cycles]	
	Late age at menopause		Increased cumulative exposure of breast tissue to stimulating hormone
	Hormone replacement therapy after menopause		
	Maternal health during pregnancy	Conditions affect intrauterine hormone levels	[Especially important during second decade of life]
	Alcohol	Hormone metabolism changes	
	Lactation	Stops menstrual cycles for some months	
	Results in long-term decreases in some hormone levels		
Obesity later in life	Hormone metabolism changes		
DDT and other pesticide (?) exposure	These collect in breast tissue and may act like extra estrogen.		
III	Late age at first full-term pregnancy (FFTP)	FFTP causes breast duct cells to divide to "terminal" duct cells which are much less sensitive to carcinogen damage.	Longer period of time during which sensitive breast duct cells can be damaged

Table 2

Description of a current national study of chemotherapy in premenopausal women with breast cancer and axillary node metastasis

A comparison of 6 treatment programs

1. Cyclophosphamide and Doxorubicin on the first day every 3 weeks for 4 treatments	followed by	Taxol every 3 weeks for 4 treatments
2. Cyclophosphamide and Doxorubicin on the first day every 3 weeks for 4 treatments		No further chemotherapy
3. Cyclophosphamide on the first day and Doxorubicin days 1 <u>and</u> 2, every 3 weeks for 4 treatments	followed by	Taxol every 3 weeks for 4 treatments
4. Cyclophosphamide on the first day and Doxorubicin days 1 <u>and</u> 2, every 3 weeks for 4 treatments		No further chemotherapy
5. Cyclophosphamide on the first day and higher dose Doxorubicin on days 1 and 2, every 3 weeks for 4 treatments and growth factor injections and antibiotic	followed by	Taxol every 3 weeks for 4 treatments
6. Cyclophosphamide on the first day and higher dose Doxorubicin on days 1 and 2, every 3 weeks for 4 treatments and growth factor injections and antibiotic		No further chemotherapy

Figure 1. Age Incidence of Breast Cancer

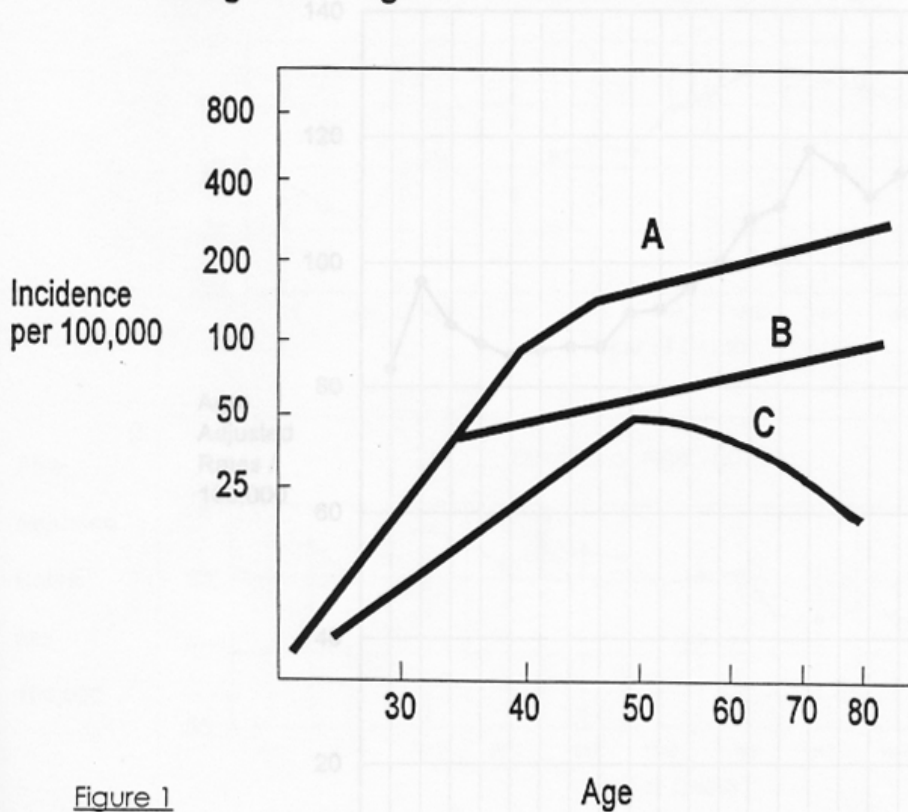


Figure 1

Curve A shows the expected rates for white American women.

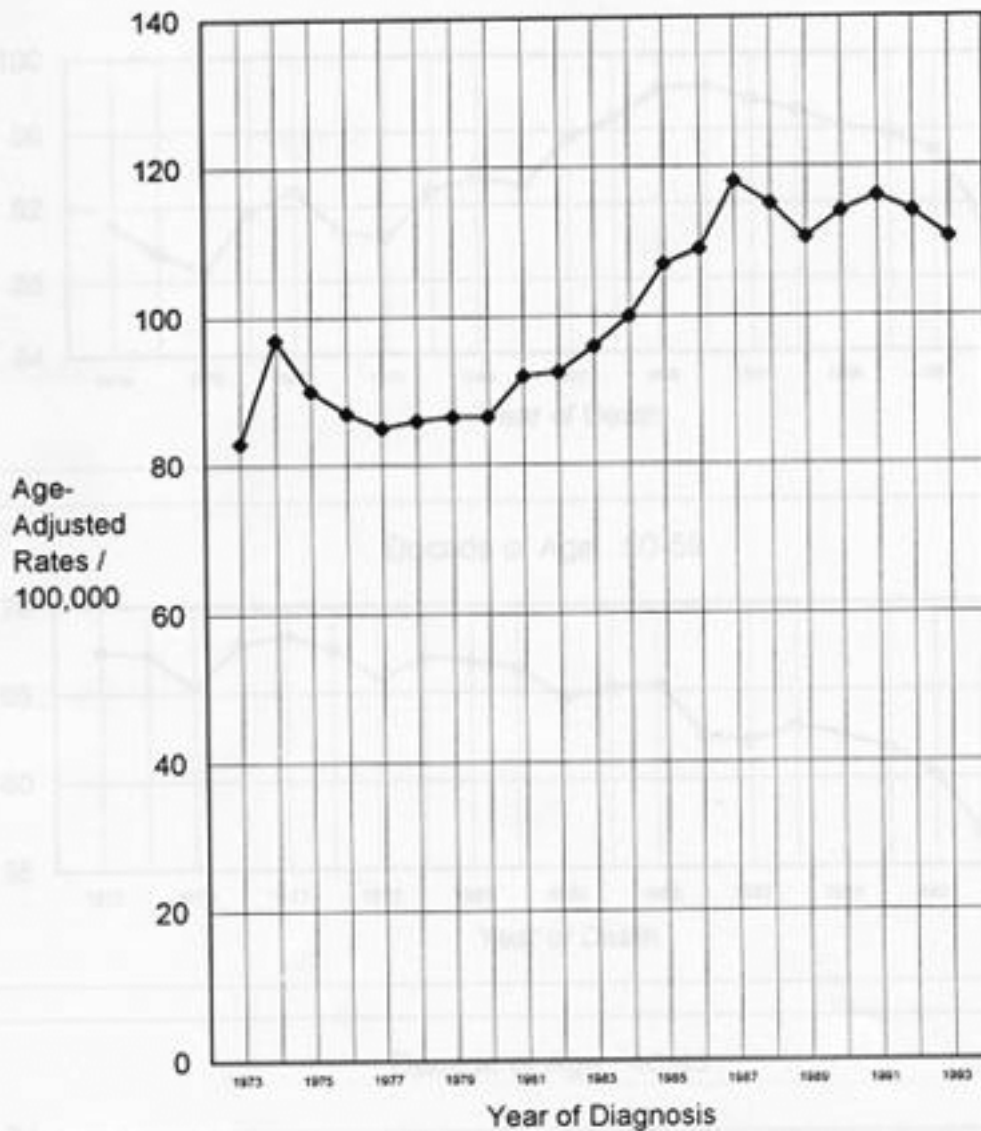
Curve B shows the projected rates for women undergoing removal of both ovaries at age 35.

Curve C shows the expected rates for many populations in Asia

Note that both axes on this graph are logarithmic, and so the absolute differences become greater as one reads left to right and down up. See text for further discussion of these curves.

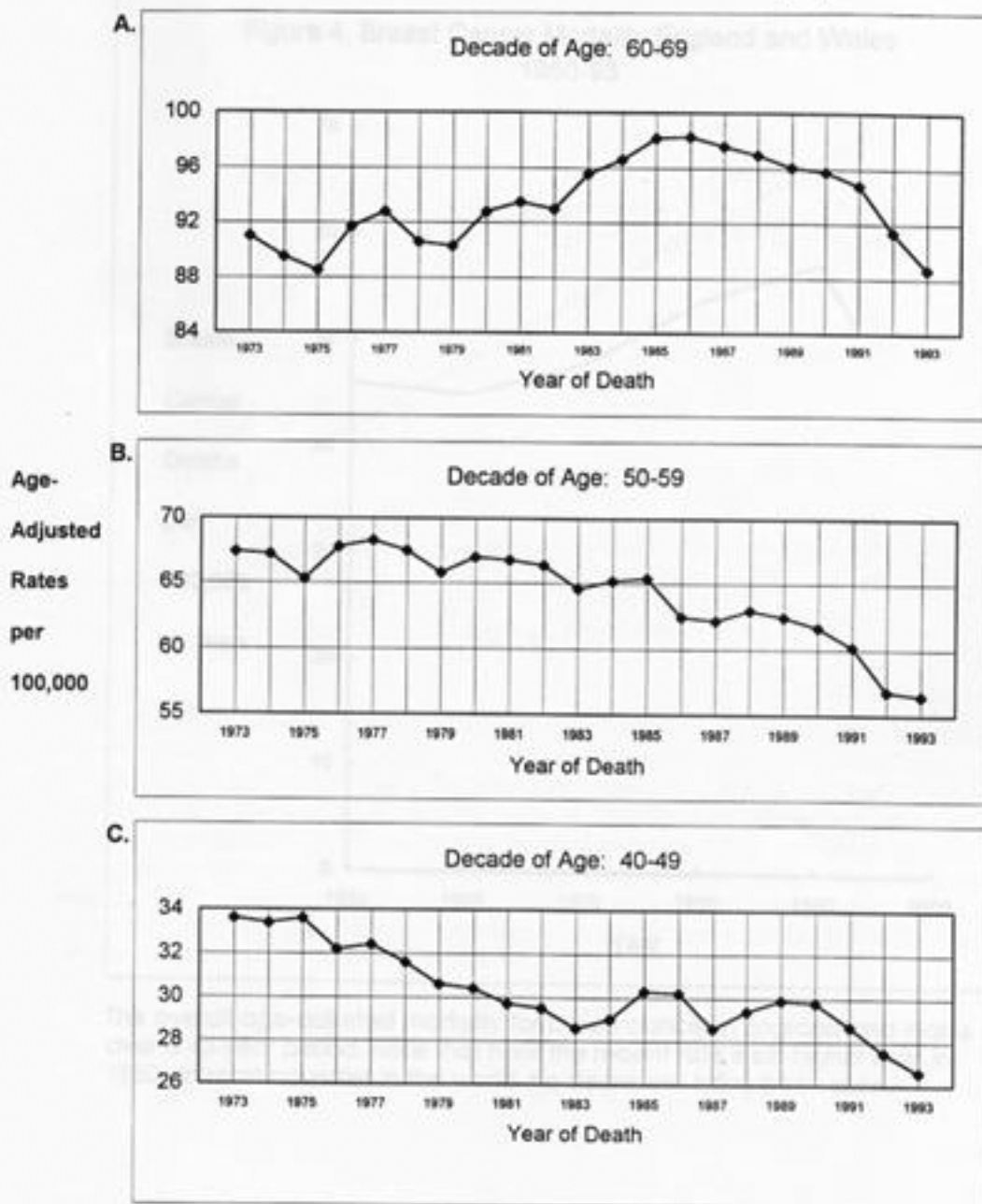
From Pike MC, British Journal of Cancer 60:142, 1989.

Figure 2. Age-adjusted breast cancer incidence (per 100,000) for White women 1973-93 (US)



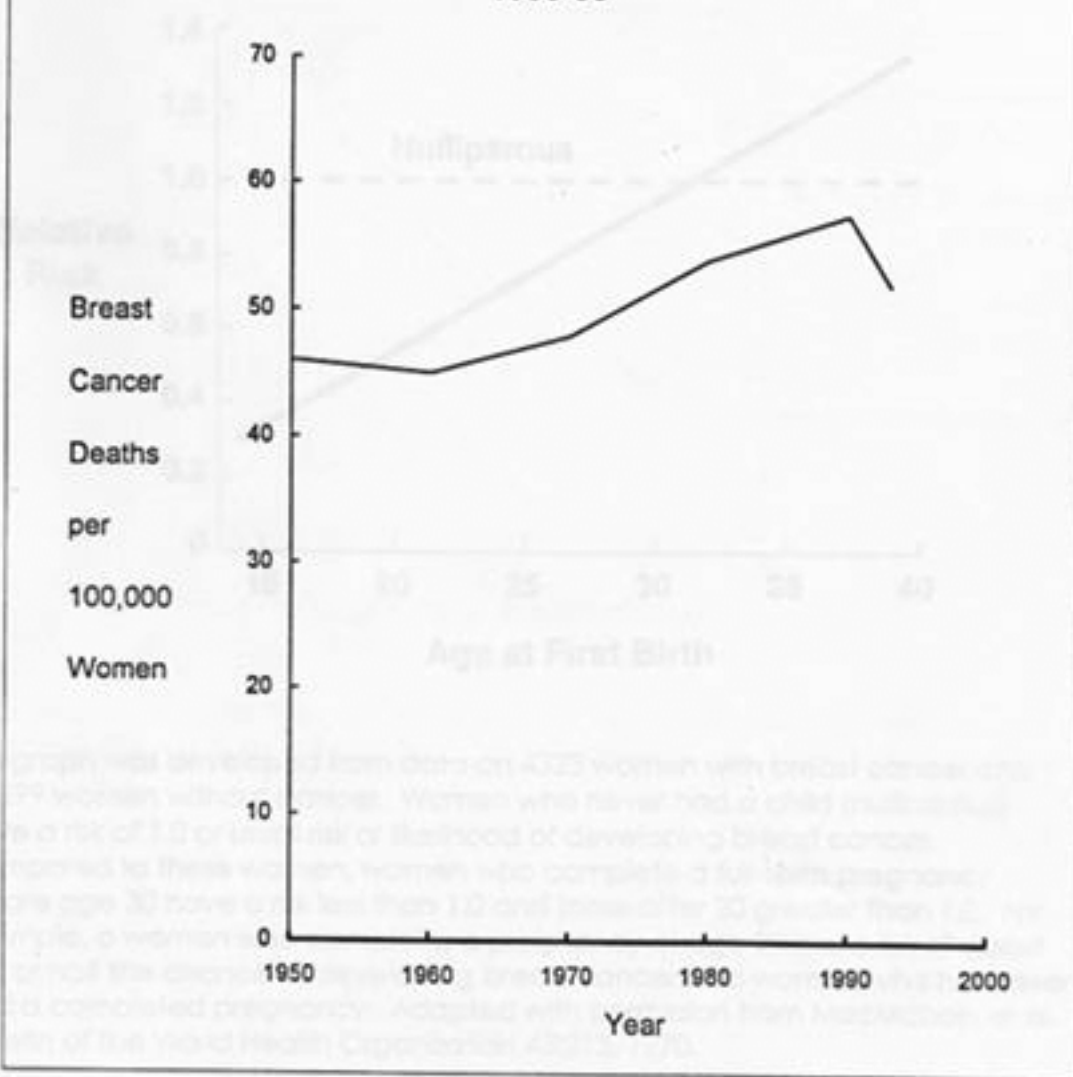
The figure provides the most accurate picture of the recent trends in breast cancer occurrence: a significant rise in the 1980s, with a recent leveling off. From the Journal of the National Cancer Institute 88:1575, 1996.

Figure 3. Age-adjusted breast cancer mortality rates by decade of age (per 100,000) for White women 1973-93 (US)



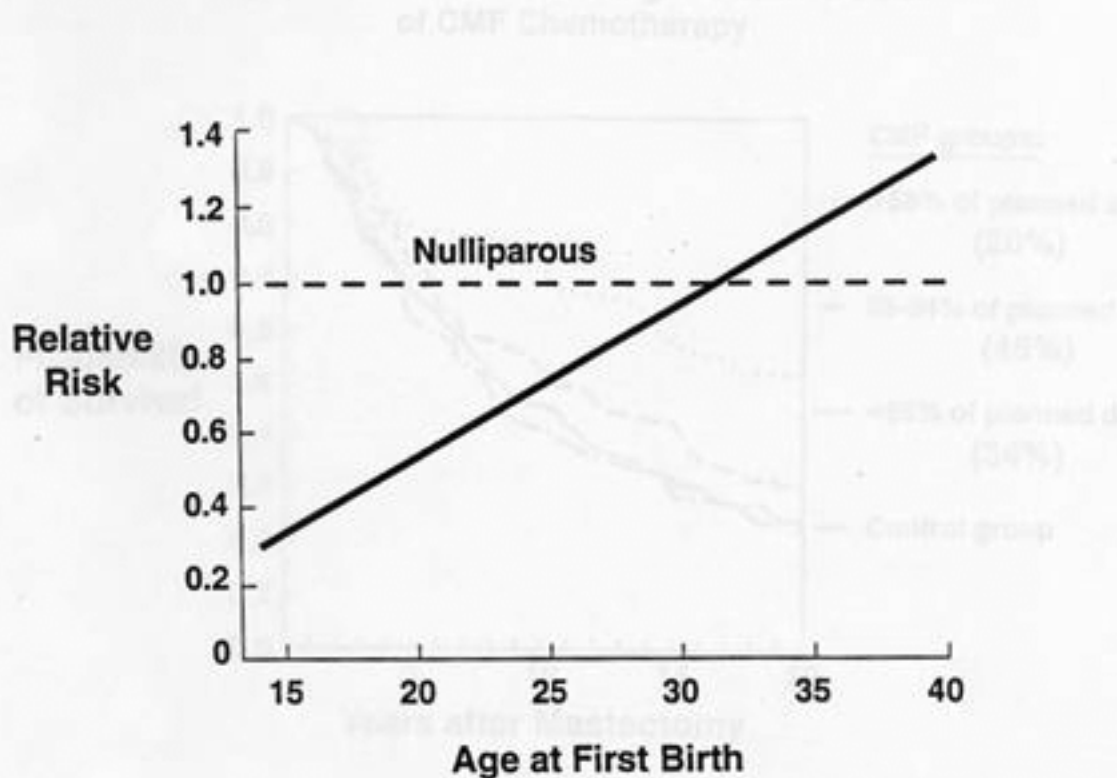
The figures show the significant recent decreases seen in breast cancer mortality for three groups of middle-aged American women. Note that the rates remain very high however. From the Journal of the National Cancer Institute 88:1574, 1996.

**Figure 4. Breast Cancer Mortality England and Wales
1950-93**



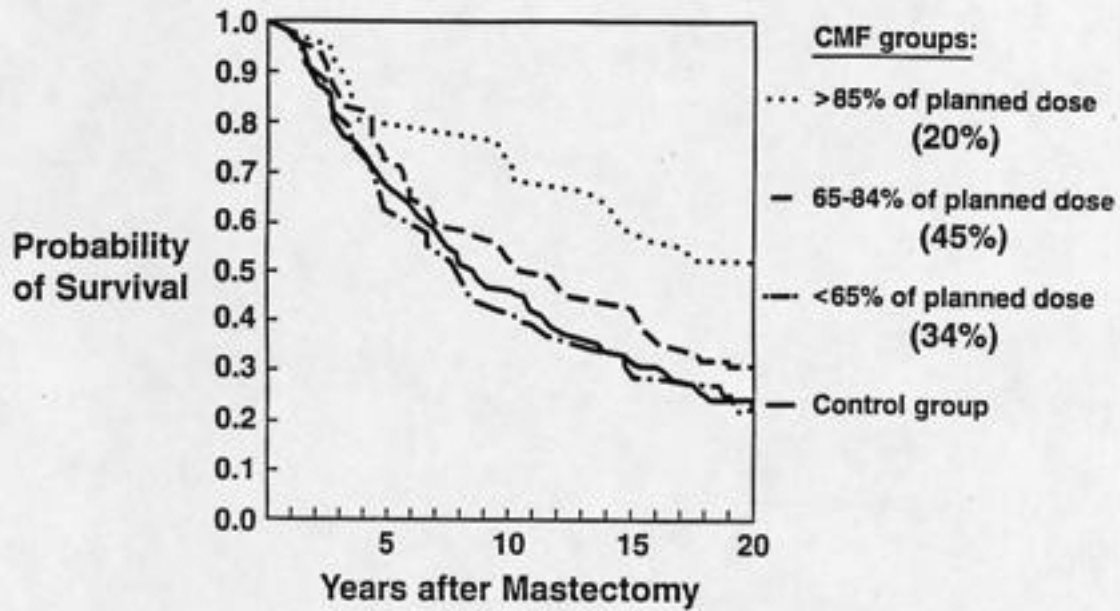
The overall age-adjusted mortality for breast cancer in England and Wales over a 43-year period. Note that here the recent rate is still higher than in 1950. In most countries in the world, no decreases have been seen.

Figure 5. Age at first full-term pregnancy and risk of breast cancer



This graph was developed from data on 4323 women with breast cancer and 12,699 women without cancer. Women who never had a child (nulliparous) have a risk of 1.0 or usual risk or likelihood of developing breast cancer. Compared to these women, women who complete a full-term pregnancy before age 30 have a risk less than 1.0 and those after 30 greater than 1.0. For example, a woman who completes a pregnancy at age 20 has a risk of about 0.5, or half the chance of developing breast cancer as a woman who has never had a completed pregnancy. Adapted with permission from MacMahon, et al. Bulletin of the World Health Organization 43:213, 1970.

Figure 6. Survival According to Planned Dose of CMF Chemotherapy



The long-term results from the standard CMF adjuvant chemotherapy treatment program. See text for explanation. From Bonadonna G. *New England Journal of Medicine* 332:904, 1995.